만성두드러기

(두드러기가 계속 있어요. 무엇을 잘못 먹은 걸까요?)

순천향대학교 서울병원 소아청소년과

민택기

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2025년 대한천식알레르기학회
제66차 알레르기 교육강좌

진료실에서 가장 많이 묻는 질문, 전문가들이 직접 답합니다.

Urticaria vs Angioedema

- Sharply circumscribed superficial central swelling of variable size and shape, almost invariably surrounded by reflex erythema
- Itching or sometimes burning sensation
- Fleeting nature, with the skin returning to its normal appearance, usually within 30 min to 24 h

- Pronounced erythematous or skin-colored deep swelling in the lower dermis and subcutis or mucous membranes
- Tingling, burning, tightness, and sometimes pain rather than itch
- Resolution slower than that of wheals (can take up to 72 h)

The EAACI/GA²LEN/EuroGuiDerm/APAACI guidelines for the definition, classification, diagnosis and management of urticaria. Allergy 2022;77(3):734-66.

Definition of Urticaria

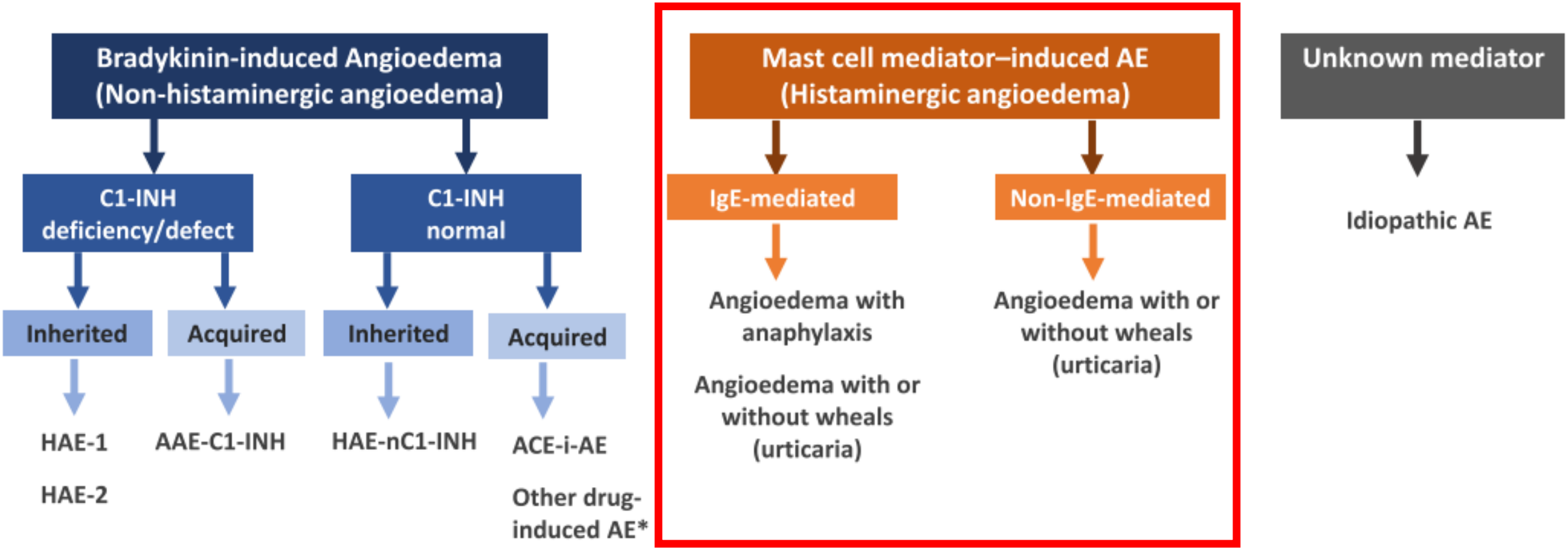
Urticaria is a condition characterized by the development of wheals (hives), angioedema or both.

- Chronic spontaneous urticaria (CSU)
  - Urticaria-predominant phenotype in 50% of patients
  - Urticaria and angioedema in 40% of patients
  - **Mainly angioedema in 10%**

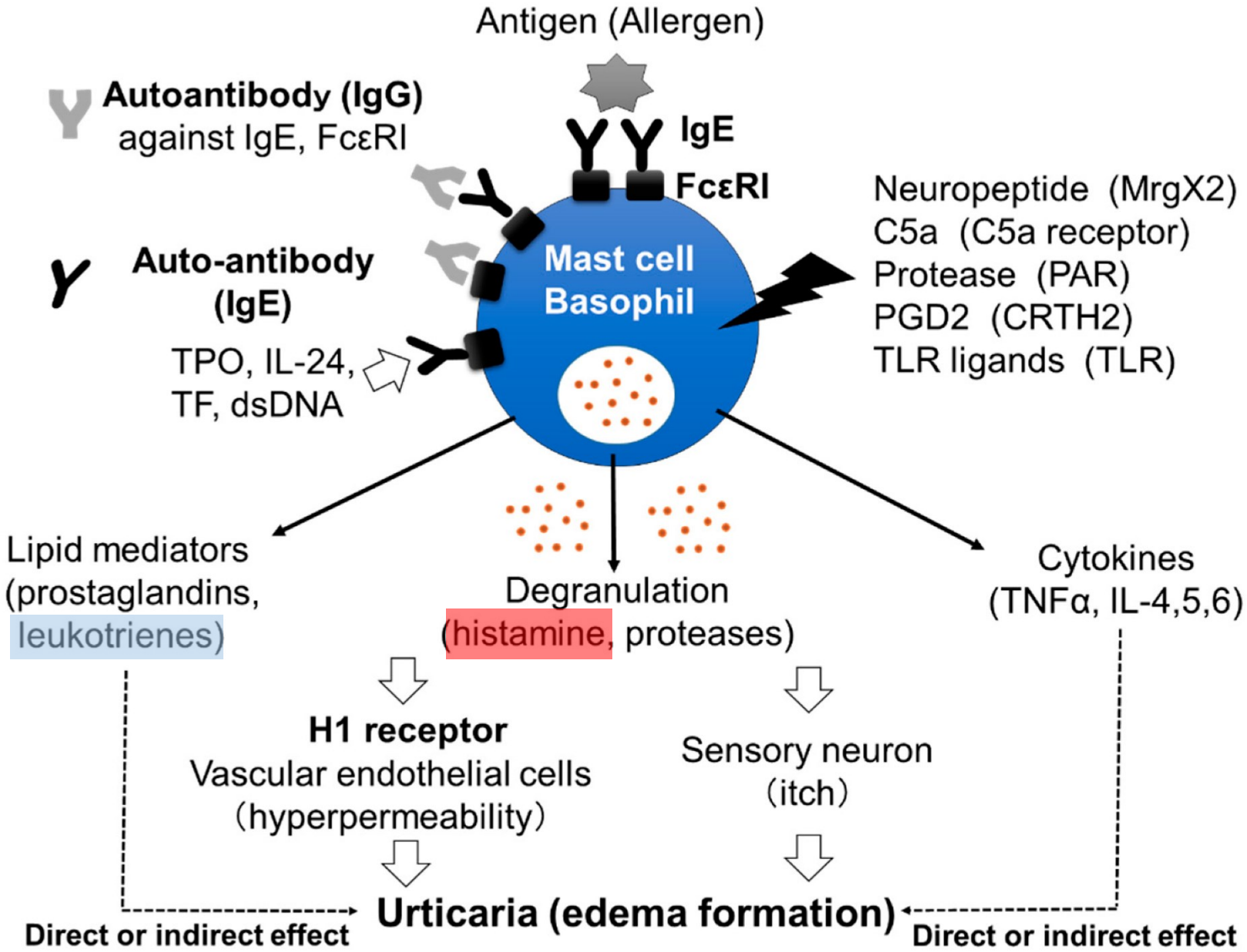
→ In 2017, isolated spontaneous angioedema without urticaria was included in the definition of CSU for the first time

The EAACI/GA²LEN/EuroGuiDerm/APAACI guidelines for the definition, classification, diagnosis and management of urticaria. Allergy 2022;77(3):734-66.

Classification of angioedema



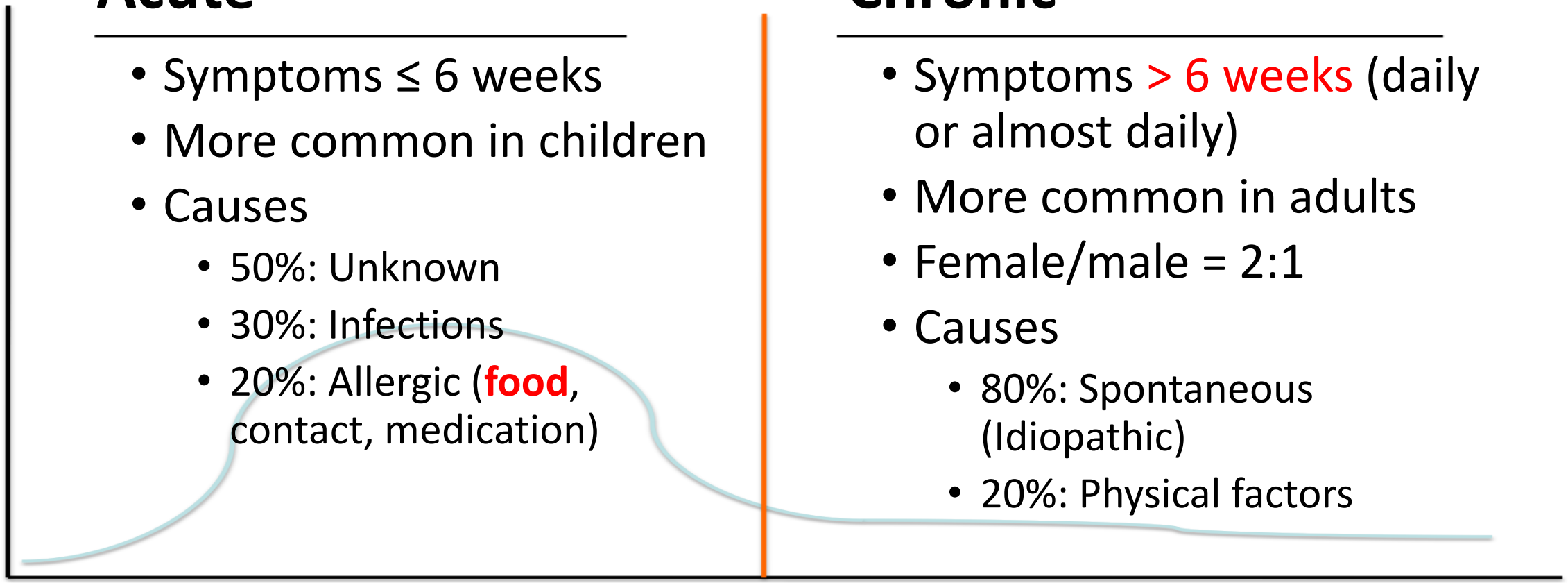
Allergy Asthma Clin Immunol 2024;20(Suppl 3):65.



Cells 2021;10(7):1759.

Urticaria: Acute vs Chronic

- **Acute**
  - Symptoms ≤ 6 weeks
  - More common in children
  - Causes
    - 50%: Unknown
    - 30%: Infections
    - 20%: Allergic (**food**, contact, medication)
- **Chronic**
  - Symptoms > 6 weeks (daily or almost daily)
  - More common in adults
  - Female/male = 2:1
  - Causes
    - 80%: Spontaneous (Idiopathic)
    - 20%: Physical factors



0

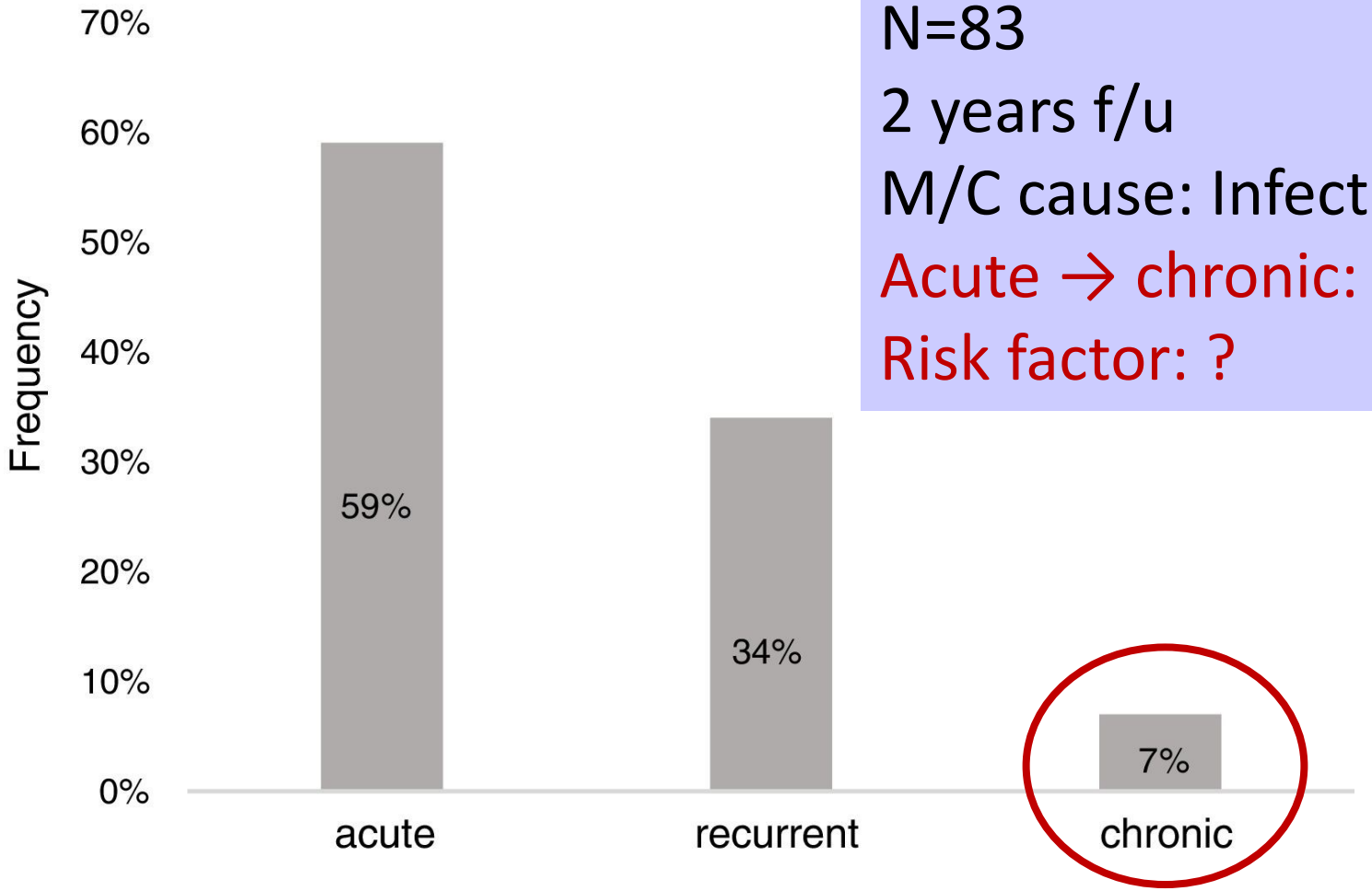
6 weeks

급성두드러기 환자중에 얼마나 만성으로 가나요?

ORIGINAL ARTICLE

Predictive factors for progression to chronicity or recurrence after the first attack of acute urticaria in preschool-age children

Pinar Gur Cetinkaya*, Ozge Soyer*, Saliha Esenboga, Umit Murat Sahiner, Ozlem Teksam, Bulent Enis Sekerel



N=83

2 years f/u

M/C cause: Infection(55.4%, URTI)

Acute → chronic: 7%

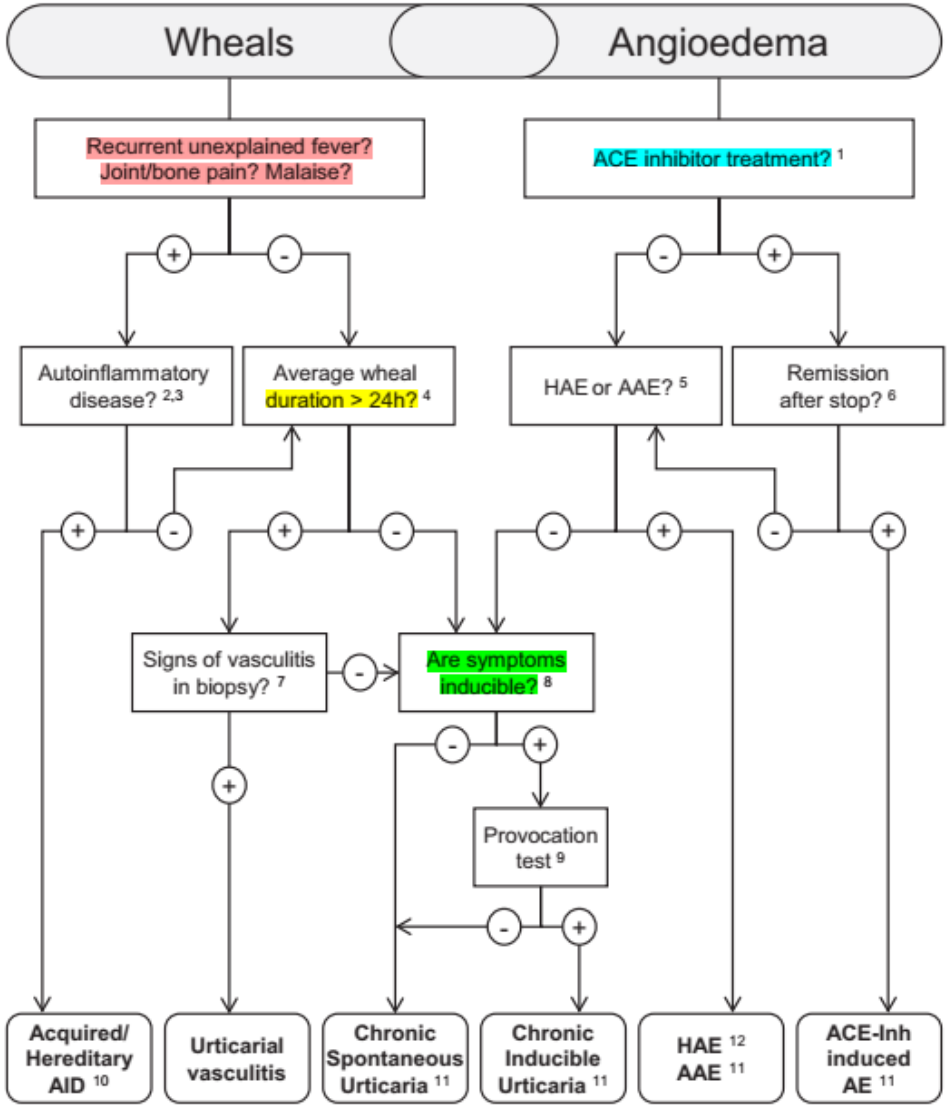
Risk factor: ?

Allergol Immunopathol (Madr) 2019;47:484-90.

Diagnosis of Urticaria

- Detailed history taking and physical examination
- Patients' documentation of signs and symptoms (including **pictures**)
  - Appearance of the lesions: wheals, evanescent, without scarring, < 24 hours in duration +/- angioedema
  - Associated features: Itch (main feature), burning (not typical)
  - Extra-cutaneous features → possible systemic disease
  - Triggers, timing of onset of symptoms, duration, response to treatment
  - Concomitant medication, diseases, atopic history

Diagnostic algorithm for chronic wheals and/or angioedema



Allergy 2022;77(3):734-66.

Diagnostic workup in Spontaneous Urticaria

Types	Subtypes	Routine diagnostic tests (recommended)	Extended diagnostic programme[a] (based on history) – For identification of underlying causes or eliciting factors and for ruling out possible differential diagnoses if indicated
Spontaneous urticaria	Acute spontaneous urticaria	None	None[b]
	CSU	Differential blood count. ESR and/or CRP IgG anti-TPO and total IgE[e]	Avoidance of suspected triggers (eg, drugs); diagnostic tests for (in no preferred order): (i) infectious diseases (eg, *Helicobacter pylori*); (ii) functional autoantibodies (eg, basophil test); (iii) thyroid gland disorders (thyroid hormones and autoantibodies); (iv) allergy (skin tests and/or allergen avoidance test, eg, avoidance diet); (v) concomitant CIndU, see below[45];(vi) severe systemic diseases (eg, tryptase); and (vii) other (eg, lesional skin biopsy)

The only exception is the suspicion of acute urticaria due to a type I food allergy in sensitized patients or drug hypersensitivity, especially for non-steroidal anti-inflammatory drugs (NSAIDs)

The EAACI/GA²LEN/EuroGuiDerm/APAACI guidelines for the definition, classification, diagnosis and management of urticaria. Allergy 2022;77(3):734-66.

• BOX 39.4 Suggested Testing for Chronic Urticaria and Angioedema of Unknown Cause

Basic Tests

- Routine screening
  - None
- Optional tests based on history and physical
  - Physical challenges
  - Complete blood count with differential
  - Erythrocyte sedimentation rate or C-reactive protein
  - Thyroid-stimulating hormone, antimicrosomal antibodies, antithyroglobulin antibodies
  - Stool for ova and parasites
  - C4, C1INH antigen, C1INH function

Discretionary Tests Based on Evaluation

- If vasculitis is suspected
  - Antinuclear antibody
  - Skin biopsy
  - CH_{50}, C3, C4
  - Rheumatoid factor
  - Cryoglobulins
- If hereditary HAE-nlC1INH is suspected:
  - *F12* mutation

Pediatric Allergy: Principles and Practice, 4th Edition

Diagnostic workup in Chronic Inducible Urticaria (CIndU)

Disorder	Trigger Factor	Test
Dermographism	Stroking, scratching, pressure	Stroking with tip of pen
Delayed pressure urticaria	Pressure 30 min to 12 hrs	Shoulder sling with 7 kg
Cholinergic urticaria	BT↑: exercise, hot water, emotion	Exercise or warm bath
Cold contact urticaria	Exposure to cold objects	Ice cube test
Heat contact urticaria	Exposure to warm objects	Application of warm water
Exercise-induced urticaria	Exercise activity	Treadmill test
Aquagenic urticaria	Contact with water	Application water for 30 min
Solar urticaria	Exposure to sunlight	Exposure to UVA, UVB or light
Vibratory urticaria	Exposure to vibrating machinery	Vortex held to skin for 10 min

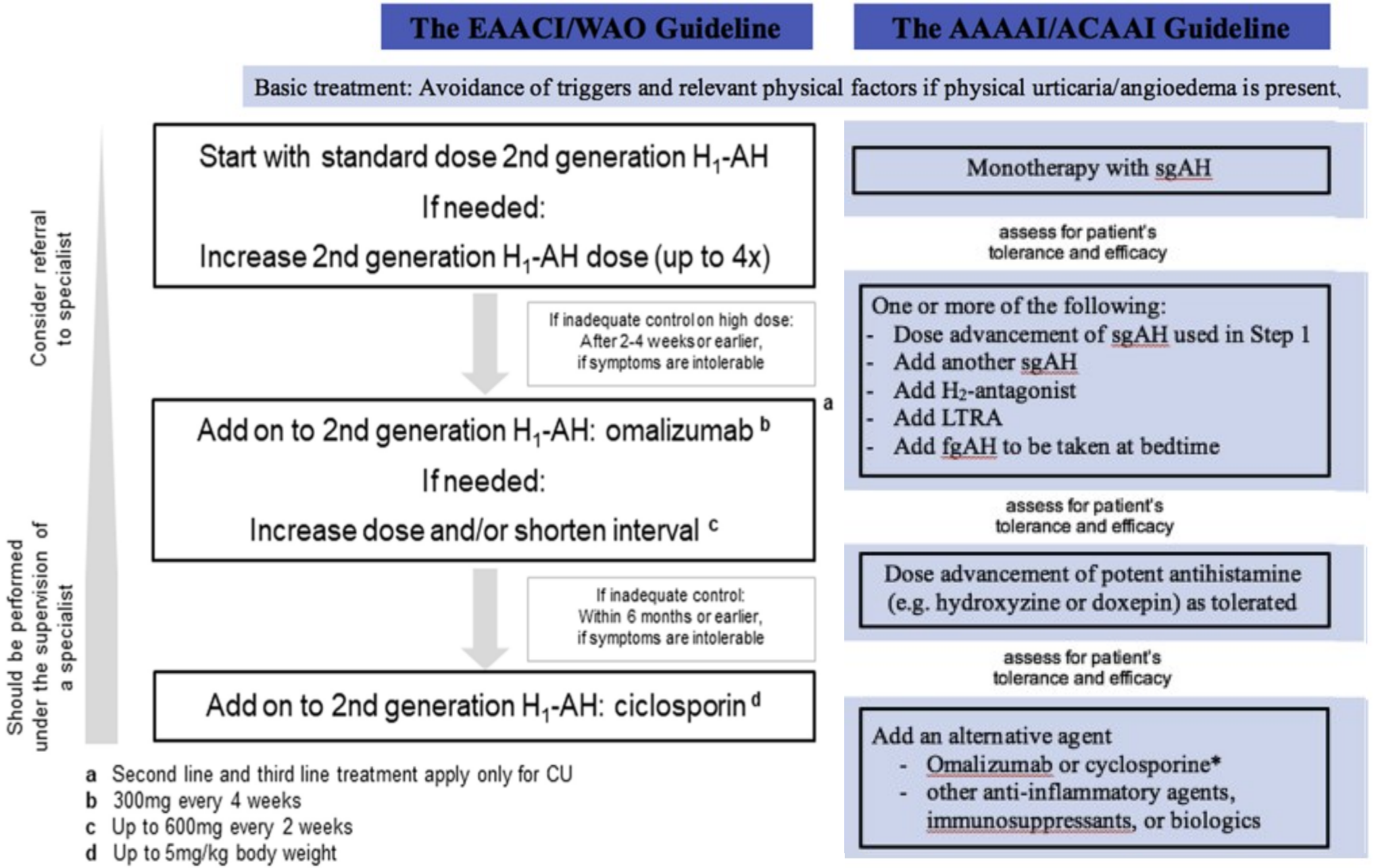
Management of Chronic Urticaria

H1-antihistamines

- 2nd generation H1-antihistamines > 1st generation H1-antihistamines
- Points to consider
  - Side effects (sedation, decreased cognitive, performance, dryness of the mouth and eyes, constipation, Worsened urinary retention , and potential provocation of narrow-angle glaucoma)
  - Lowest licensed age

2nd generation H1-antihistamines

- Azelastine (아젭틴) - 6세 이하 금기
- Bepotastine (타리온, 베리온) – 소아 안전성 확립 x
- Cetirizine (지르텍) - 2세 미만 금기, Levocetirizine (씨잘) - 1세 미만 금기
- Loratadine(클라리틴) - 2세 미만 금기, Desloratadine (에리우스) - 1세 미만 금기
- Ebastine (에바스텔) - 2세 미만 안전성 확립 x
- Fexofenadine (알레그라) - 6세 미만 안전성 확립 x
- Ketotifen (자디텐, 케토티펜) - 6개월 미만 용량 x
- Mizolastine (미졸렌) - 12세 미만 안전성 확립 x
- Rupatadine (루파핀정) - 12세 미만 안전성 확립 x



JACIP 2018;6:1144-51.
Allergy 2022;77:734-66.

Allergy Asthma Immunol Res. 2020 Jul;12(4):563-578
https://doi.org/10.4168/aair.2020.12.4.563
pISSN 2092-7355·eISSN 2092-7363

Allergy, Asthma & Immunology Research AAIR

Review

The KAAACI/KDA Evidence-Based Practice Guidelines for Chronic Spontaneous Urticaria in Korean Adults and Children: Part 1. Definition, Methodology and First-line Management

H1AH as the first-line therapy for CSU

Regimen	Recommendation (evidence level)
· **Non-sedating H1AH** (than sedating H1AH)	· **Strong (moderate)**
· **Up-dosing H1AHs up to 4-fold** (if not improved with standard dose H1AH)	· **Strong (low)**
· Combination of H1AHs (if not improved with standard dose H1AH)	· Conditional (very low)
· Regular use of H1AHs (than as needed use)	· Conditional (very low)

Add-on therapy (if not improved by H1AHs)

Drugs	Recommendation (evidence level)
· **Omalizumab**	· **Strong (moderate)**
· Cyclosporine	· Conditional (low)
· H2AHs	· Conditional (low)
· LTRAs	· Conditional, *against* (low)
· Dapsone	· Conditional, *against* (low)
· Methotrexate	· Conditional, *against* (very low)
· Phototherapy	· Conditional (very low)
· **Systemic corticosteroids**	· **Strong, *against* (very low)**

AAIR 2020;12(4):563-78.

항히스타민제는

매일 or 증상이 있을때만

먹는다.

다른 종류의

2세대 항히스타민제는

동시에 or 따로

먹는다.

만성두드러기에서 증상 조절을 위해 항히스타민제를 언제까지 사용해야 하나요?

Urticaria Control Test (UCT): 0-16 점

Instructions: You have urticaria. The following questions should help us understand your current health situation. Please read through each question carefully and choose an answer from the five options that *best fits* your situation. Please limit yourself to *the last four weeks*. *Please don't think about the questions for a long time*, and do remember to answer *all questions* and to provide *only one answer to each question*.

1. How much have you suffered from the **physical symptoms of the urticaria (itch, hives (welts) and/or swelling)** in the last four weeks?

   O very much O much O somewhat O a little O not at all

2. How much was your **quality of life** affected by the urticaria in the last 4 weeks?

   O very much O much O somewhat O a little O not at all

3. How often was the **treatment** for your urticaria in the last 4 weeks **not enough** to control your urticaria symptoms?

   O very often O often O sometimes O seldom O not at all

4. **Overall**, how well have you had your urticaria **under control** in the last 4 weeks?

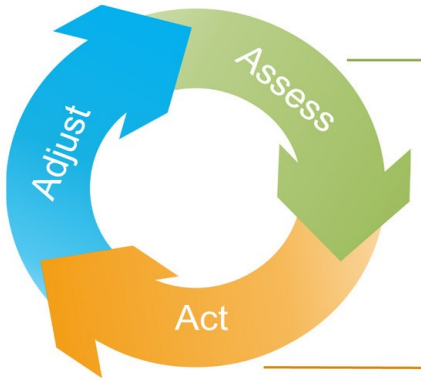
   O not at all O a little O somewhat O well O very well

0

4

Allergy 2022;77:734-66.

Chronic urticaria: Management decisions and treatment adjustments*



ADJUST
- Step up If inadequate control
- Change if side effects occur
- Step down if symptom free for 3-6 months

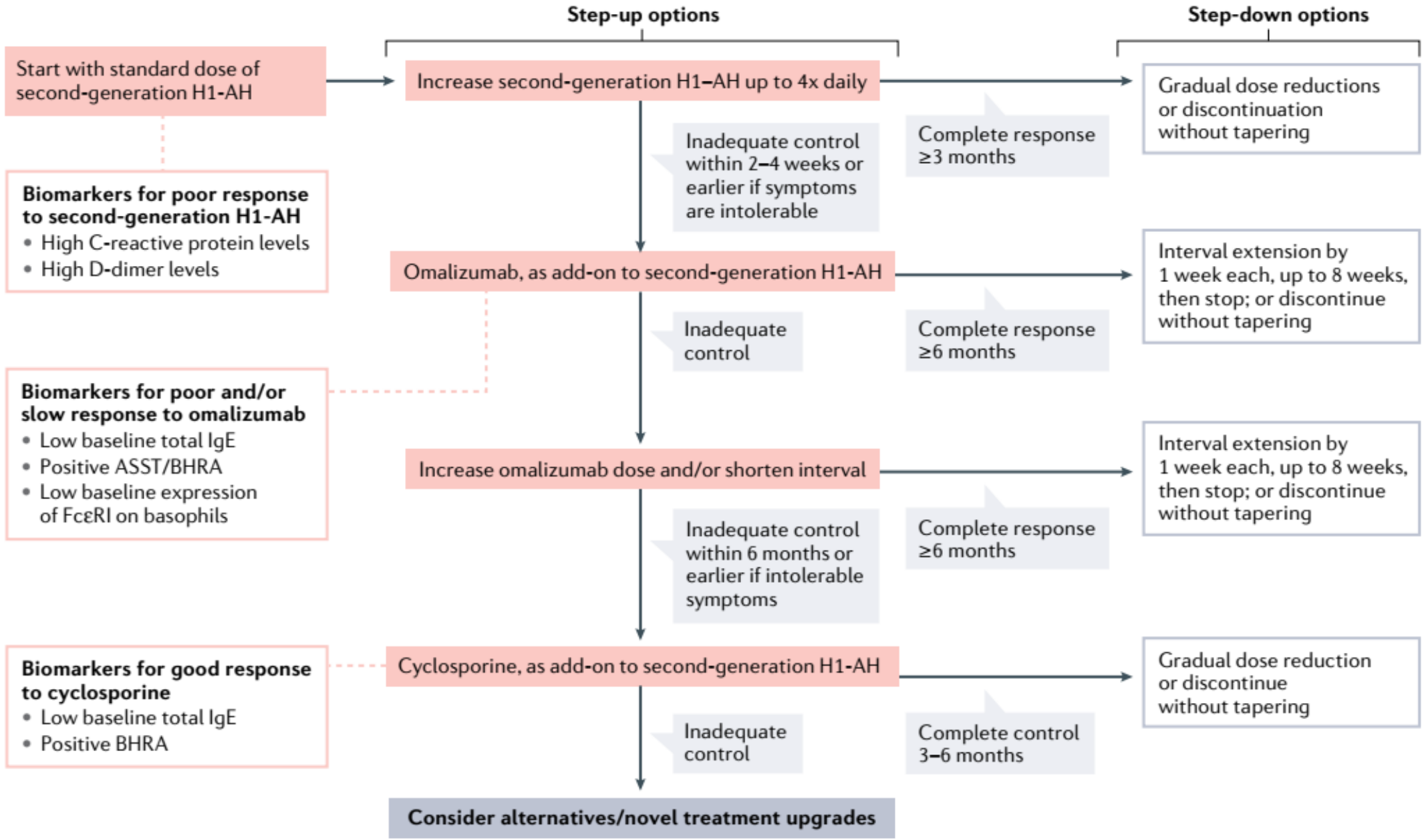
ASSESS
- Diagnostic procedures
- Comorbidities
- Severity – use UCT and PROMs
- Patient preferences
- Side effect of treatment

ACT
- Modify treatment and treat comorbidities
- Look at non-pharmacological interventions esp. in CIndU
- Educate the patient

UCT score	UCT < 12	UCT = 12-15	UCT = 16
Control level	Uncontrolled	Well-controlled	Completely controlled
Action	**Step-up* if:** - On 1-4 fold 2gAH > 7-28d - On OMA > 3m	Continue therapy and try to optimize	**Step-down*** based on individual factors by reducing dose or extending intervals

* For CIndU individual decisions are based on estimated trigger exposure (e.g. cold-urticaria in winter)

Allergy 2022;77:734-66.



Nat Rev Dis Primers 2022;8:61.

만성두드러기 증상 조절에 더 효과적인 항히스타민제가 있나요?

Table I. Efficacy of histamine H_1 receptor antagonist randomized, double-blind, placebo-controlled studies

Study	N	Duration, weeks	Treatment	Comments
Breneman et al[9]	187	4	Cetirizine 10 mg vs astemizole* 10 mg vs placebo	Cetirizine was superior to astemizole in reducing the number of wheals Both agents were statistically superior to placebo at relieving CSU symptoms based on weekly patient rating
Nettis et al[10]	100	6	Levocetirizine 5 mg vs placebo	Complete symptom resolution in 53% of patients taking levocetirizine at the study endpoint compared with 0% in the placebo group
Finn et al[11] and Nelson et al[12]	489 and 418	4	Fexofenadine 20, 60, 120, and 240 mg† and placebo	Same study design for both trials Efficacy results were similar in the 60-, 120-, and 240-mg groups. All dosages were statistically superior to placebo and the 20-mg group in reducing mean pruritus score, mean number of wheals, and mean TSS when compared to baseline values
Kaplan et al[7]	255	4	Fexofenadine 180 mg vs placebo	Once-daily dosing of fexofenadine was superior to placebo for improvement in mean number of wheals, pruritus severity scores, and in TSS
Handa et al[13]	97	4	Cetirizine 10 mg vs fexofenadine 180 mg	Cetirizine showed superior overall efficacy, determined by subject rating on an analog scale Complete symptom resolution in 52% of patients taking cetirizine at the study endpoint compared with 4.4% in the fexofenadine group
Leynadier et al[14]	61	4	Mizolastine 10 mg vs loratadine 10 mg	Both agents had a similar reduction in urticarial episodes Mizolastine was associated with a greater reduction in the number of wheals compared to loratadine
Ortonne et al[3]	137	6	Desloratadine 5 mg vs placebo	Desloratadine was superior to placebo in improving pruritus scores

J Am Acad Dermatol 2018;79:617-33.

항히스타민제 용량에 따라 증상이 조절되는 환자의 비율은 어떻게 되나요?

Refractory CSU?

Standard doses of H1-antihistamines:

50% non-responders[1] (50)

Updosing of H1-antihistamines:

38.6% non-responders[2] (19)

Omalizumab:

32% non/partial-responders[3] (6)

1. van den Elzen MT, et al. Clin Transl Allergy 2017;7:4.
2. Guillén-Aguinaga S, et al. Br J Dermatol 2016;175(6):1153-65.
3. Bernstein JA, et al. Expert Opin Biol Ther 2018;18:425-48.

Asia Pacific allergy
pISSN 2233-8276 · eISSN 2233-8268
Original Article
http://dx.doi.org/10.5415/apallergy.2016.6.1.16
Asia Pac Allergy 2016;6:16-28

A stepwise approach in the management of chronic spontaneous urticaria in children

Xin Hui Magdeline Lee[1], Lin Xin Ong[2], Jing Yi Vanessa Cheong[1], Rehena Sultana[3], Rajeshwar Rao[2], Hwee Hoon Lim[2], Xiao Mei Ding[2], Wen Yin Loh[2], Monika Punan[1], and Wen Chin Chiang[2,*]

Table 1. Algorithm for weight based antihistamine dosing titration in children

Antihistamine	Child's weight (kg)	Child's age (yr)	Total daily recommended dose (mg)			
			Step 1	Step 2	Step 3	Step 4
Cetirizine*	≤9.9		2.5	5	7.5	15
	10–19.9		5	10	15	20
	20–29.9		7.5	15	22.5	30
	≥30		10	20	30	40
Levocetirizine†	≤9.9		1.25	2.5	3.75	5
	10–19.9		2.5	5.0	7.5	10
	20–29.9		3.75	7.5	11.25	15
	≥30		5	10	15	20
Desloratadine‡	≤9.9		1	2.0	3	4
	10–19.9		1.25	2.5	3.75	5
	20–29.9		2.5	5	7.5	10
	≥30		5	10	15	20
Fexofenadine§		0.5–<2	30	60	90	120
		2–11	60	120	180	240
		≥12	120 (180)	240	360	360

Asia Pac Allergy 2016;6:16-28.

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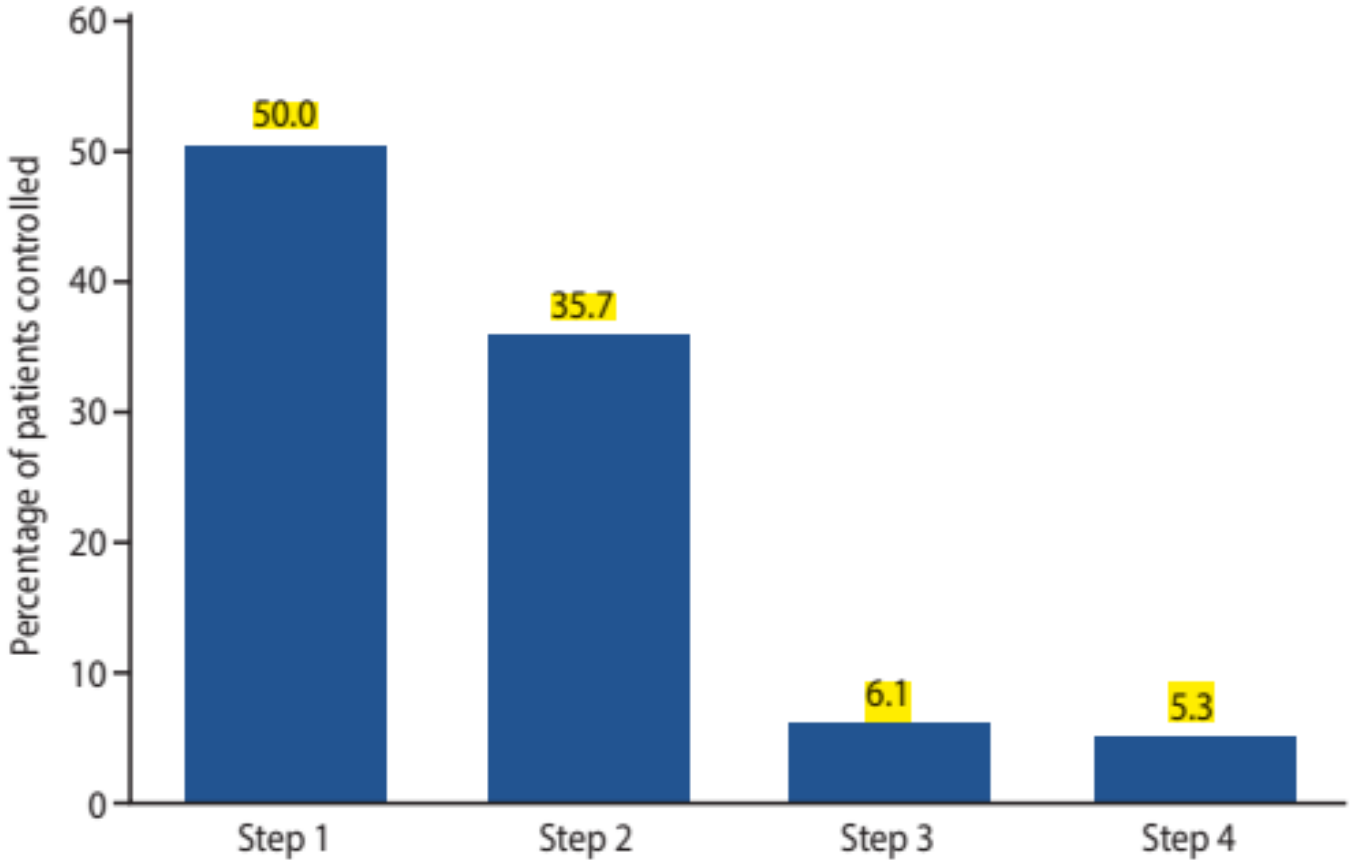
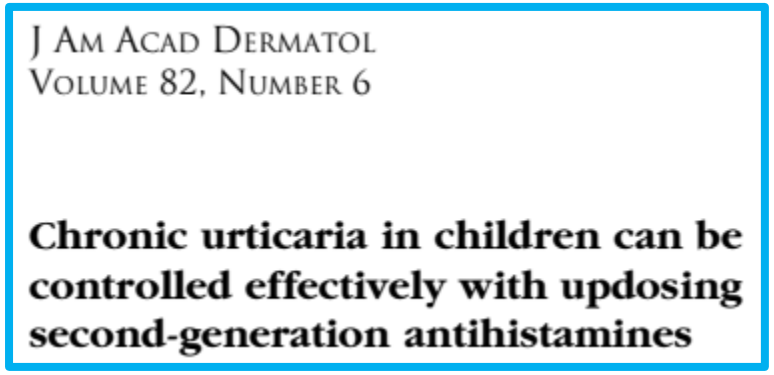


Asia Pac Allergy 2016;6:16-28.

Efficacy and tolerability of the updosing of sgAH in children with CU


J Am Acad Dermatol
Volume 82, Number 6

Chronic urticaria in children can be controlled effectively with updosing second-generation antihistamines

Standard dose ~ up to fourfold dose

92%

J Am Acad Dermatol 2020;82:1535-37.


ORIGINAL ARTICLE

WILEY

Efficacy and tolerability of the updosing of second-generation non-sedating H1 antihistamines in children with chronic spontaneous urticaria

Lucrezia Sarti | Simona Barni | Mattia Giovannini | Giulia Liccioli | Elio Novembre | Francesca Mori

Standard dose: 37.9%

Double dose: 24.3%

Threefold dose: 3.0%

Fourfold dosse: 1.5%

Total : 66.7%

Pediatr Allergy Immunol 2021;32:153-60.

Leukotriene receptor antagonists as add-on therapy to antihistamines for urticaria: Systematic review and meta-analysis of randomized clinical trials

Daniel G. Rayner, BHSc,[a] Ming Liu, BSc,[a,b] Alexandro W. L. Chu, BHSc,[c] Xiajing Chu, MPH,[a] Gordon H. Guyatt, MD,[a,c] Paul Oykhman, MD, MSc,[c] Daniel J. Cao, BSc,[c] Joseph Moellman, MD,[d] Moshe Ben-Shoshan, MD, MSc,[e] Diane R. Baker, MD,[f] Susan Waserman, MD, MSc,[c] David Lang, MD,[g] Javed Sheikh, MD,[h] Sameer K. Mathur, MD, PhD,[i] Lisa A. Beck, MD,[j] David A. Khan, MD,[k] Eric T. Oliver, MD,[l] Rachel N. Asiniwasis, MD,[m] Emily F. Cole, MD, MPH,[n] Kathryn E. Wheeler, MD,[o] Lauren Runyon, MSN,[k] Jeffrey Chan, MD,[p] Kathryn P. Trayes, MD,[q] Sanaz Eftekhari, BA,[r] Donna D. Gardner, DrPH,[s] Tonya Winders, MBA,[t] Sarbjit S. Saini, MD,[l] Jonathan A. Bernstein, MD,[u] and Derek K. Chu, MD, PhD[a,c,v]

Arlington and Fairfax, Va; Baltimore, Md; Cincinnati and Cleveland, Ohio; Dallas, Tex; Durham, NC; Gainesville, Fla; Hamilton and Newmarket, Ontario, Montreal, Quebec, and Regina, Saskatchewan, Canada; Lanzhou, China; Los Angeles, Calif; Madison, Wis; Philadelphia, Pa; Portland, Ore; Rochester, NY; and Vienna, Austria

JACI 2024;154(4):996-1007.

Leukotriene Receptor Antagonists as Add-on Therapy to Antihistamines for Urticaria

A Systematic Review and Meta-Analysis of Randomized Clinical Trials

34 RCTs

3 324 Participants

Age Groups
Pediatric + Adult

Urticaria Type
Spontaneous + Inducible

Intervention
LTRA Added to H1-Antihistamines

Comparator
H1-Antihistamines Alone

- Disease Activity
- Sleep Disturbance
- Itch Severity
- Quality of Life
- Wheal Severity
- Adverse Events

Main Findings GRADE

Number Needed to Treat

Urticaria Disease Activity

8

Moderate Certainty

Similar findings for itch, wheal, and quality of life

Number Needed to Harm

Neuropsychiatric Adverse Events

161

Low Certainty

No difference in overall adverse events

Conclusions

In the management of urticaria, the addition of leukotriene receptor antagonists to H1-antihistamines probably provides a small, potentially patient-unimportant, reduction in urticaria activity with little to no difference in overall adverse events. We observed similar findings for itch severity, wheal severity, and quality of life.

The risk of neuropsychiatric adverse events from leukotriene receptor antagonists in patients with urticaria is small and uncertain.

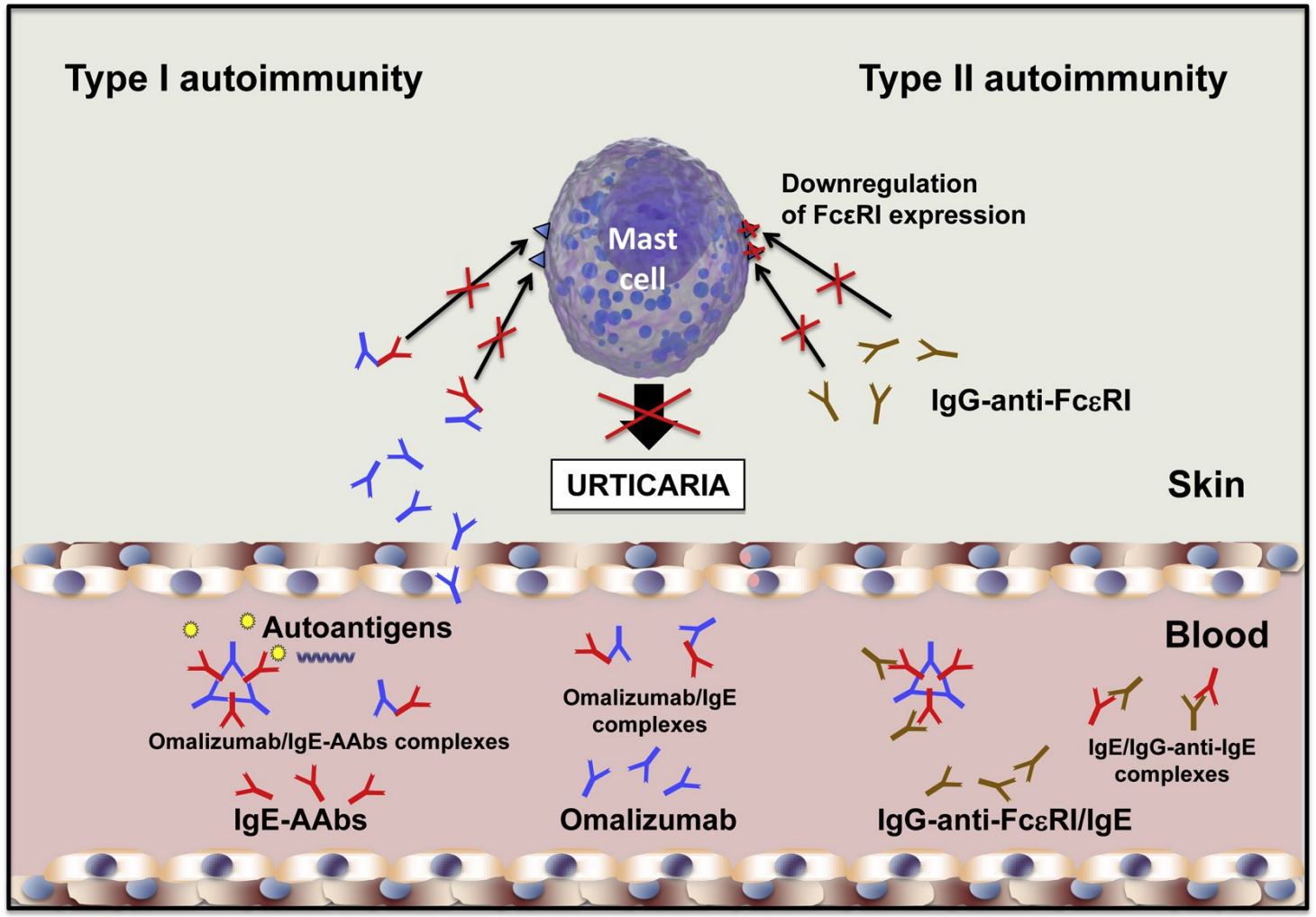
EVIDENCE in ALLERGY

JOINT TASK FORCE ON PRACTICE PARAMETERS JTF PP

GRADE: Grading of Recommendations Assessment, Development and Evaluation; LTRA: Leukotriene receptor antagonist; RCT: Randomized controlled trial.

JACI 2024;154(4):996-1007.

Omalizumab in children with CU(12세 이상)



J Allergy Clin Immunol 2014;5:1270-7.

Omalizumab in children with CU(12세 이상)

졸레어

옴리클로

만성두드러기는 얼마나 오래 지속되나요?

Natural History and Prognosis in children

- US: 19%, 54%, and 68% at 1, 3, and 5 years
- Italy: 29%, 55%, and 72% at 1, 3, and 5 years
- Turkey: 16.5%, 38.8%, and 50% at 1, 3, and 5 years
- Thailand: 18.5%, 54%, and 67.7% at 1, 3, and 5 years
- Canada: 10.3% per year
- Korea: 33.4%, 53.0%, and 71.2% at 0.5, 1, and 2 years

Pediatr Allergy Immunol 2021;32:201-4.

Int Arch Allergy Immunol 2011;156:224–30.

J Am Acad Dermatol 2014;71:663-8.

Allergol Immunopathol (Madr) 2016;44:537-41.

JAMA Dermatol 2017;153:1236-42.

Asian Pac J Allergy Immunol 2019;37:19-24.

Targeted pathways and receptors in CSU

IgE and activating receptors

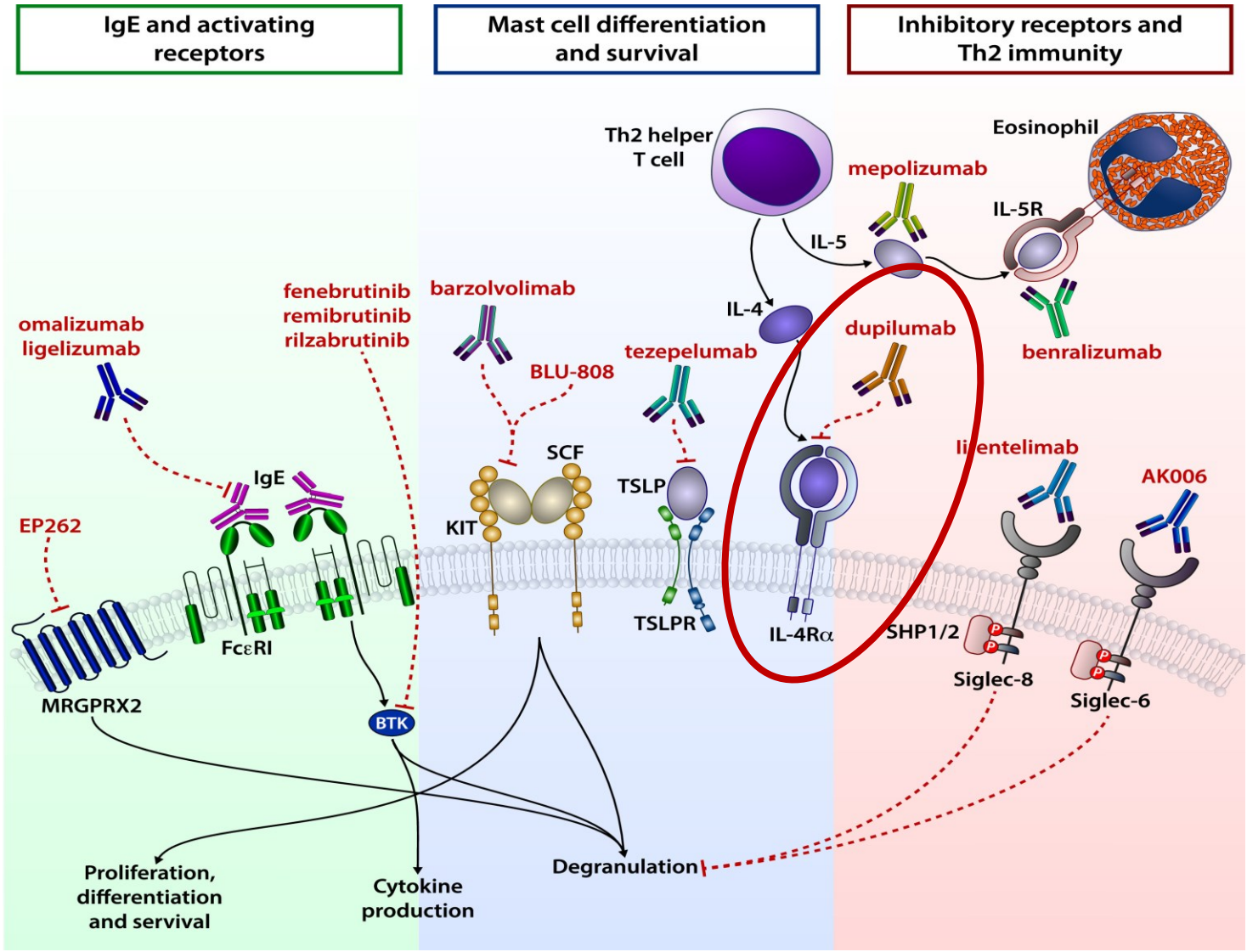
- Anti-IgE → Ligelizumab
- BTK inhibitors → Remibrutinib
- MRGPRX2 → EP262

Mast cell differentiation and survival

- Anti-KIT → Barzolvolimab

Inhibitory receptors and Th2 immune responses

- Anti-IL-4α → Dupilumab
- Anti-Siglec 8 → Lirentelimab
- Anti-TSLP → Tezepelumab
- Anti-IL5R → Benralizumab



Min TK, et al. Ann Allergy Asthma Immunol 2024;133(4):367-73.

Dupilumab in patients with chronic spontaneous urticaria (LIBERTY-CSU CUPID): Two randomized, double-blind, placebo-controlled, phase 3 trials

Marcus Maurer, MD, Thomas B. Casale, MD, Sarbjit S. Saini, MD, Moshe Ben-Shoshan, MD, Ana M. Giménez-Arnau, MD, PhD, Jonathan A. Bernstein, MD, et al

JACI 2024;154:184-94.

Dupilumab in patients with chronic spontaneous urticaria (LIBERTY-CSU CUPID): Two randomized, double-blind, placebo-controlled, phase 3 trials

METHODS

CUPID Study A

138 patients

Aged ≥ 6 years

Omalizumab-naïve

The primary and key secondary endpoints were changes from BL to week 24 in UAS7[a] and ISS7[b] respectively, or vice versa depending on regional regulatory requirements.

CUPID Study B

108 patients

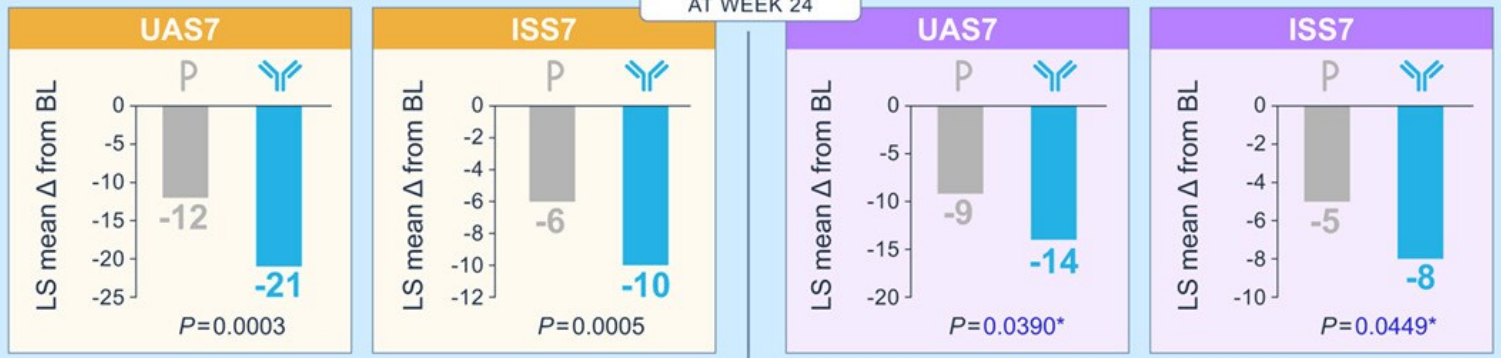
Aged ≥ 12 years

Omalizumab-intolerant/ incomplete responders

SAFETY OUTCOMES:

- Pooled safety data were consistent between dupilumab and placebo and with the known dupilumab safety profile.

RESULTS AT WEEK 24



In Study A, both UAS7 and ISS7 improved significantly with dupilumab vs placebo at week 24.

In Study B, UAS7 improved significantly (primary endpoint for EU countries), with a numerical, non-significant trend of improvement in ISS7 (primary endpoint for non-EU countries).

*Significance was tested at alpha 0.043 after the protocol pre-specified efficacy statistical criteria for futility was met. UAS7 was statistically significant (primary endpoint for EU countries); ISS7 did not meet significance (primary endpoint for non-EU countries).

P Placebo

Dupilumab

BL Baseline

EU European Union

LS Least squares

Δ Change

[a] UAS7: Urticaria Activity Score over 7 days (range: 0-42).

[b] ISS7: Itch Severity Score over 7 days (range: 0-21).

*Japan approved dupilumab for CSU in February 2024.

JACI 2024;154:184-94.

Take home messages

- 문진과 신체진찰이 분류와 감별에 중요함(무분별한 알레르기 검사 X)
- 전신증상 동반, 24시간 이상 지속, 흔적을 남기는 경우 다른 질환 감별필요
- 2세대 항히스타민제 4배까지 증량 가능
- Cetirizine, Levocetirizine 이 효과 좋음
- 만성두드러기는 1년 지날때 마다 50%정도 관해
- 다른 종류 항히스타민제, H_2 antagonist, 류코트리엔 조절제 등 조합 가능